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HIV infection with haemolytic anaemia

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Case Report *(Dr A D Sukthankar)*
A 45 year old male from Malawi was admitted in 1995 under a general medical firm with severe anaemia and uraemia. The patient had tested HIV antibody positive in early 1994 (his CD4 lymphocyte count was 0·24 × 10⁹/l at that time) and had probably acquired the infection heterosexually. He had remained asymptomatic since diagnosis and was seen in the out-patient clinic two weeks prior to admission after defaulting from the clinic for over a year. Routine blood tests on this visit indicated hyperkalaemia (6·1 mmol/l), anaemia (Hb 7·3 g/dl) and uraemia (urea 7·8 mmol/l, creatinine 152 μmol/l) with a CD4 count of 0·184 × 10⁹/l. He also complained of a pruritic rash which was settling with anti-scabies treatment. He defaulted again and subsequently presented to the general physicians at another hospital.

Day 1 On admission his main complaints were of lethargy, recurrent hiccup, nausea, diarrhoea, shortness of breath on exertion and weight loss of two weeks duration. He had been febrile without chills, rigors or night sweats. There was no history of haemoptysis, haematemesis or malaena. He had no urinary symptoms. He was known to suffer from hypertension and gout and had taken α-methyldopa and allopurinol in the past. However, he had stopped all medications for the last four months. He was married and had four children who were all well.

On examination he was afebrile and clinically anaemic. His pulse was 140/min, blood pressure was normal and he had persistent hiccup. There was no lymphadenopathy and his skin showed retro-auricular induration in addition to Kaposi's sarcoma lesions on the left hand and penis. His liver was just palpable and non-tender. His spleen was palpable about 2 cm below the costal margin. The jugular venous pressure was 2 cm above the sternal angle. On auscultation bilateral basal crepitations and a systolic flow murmur were heard.

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Laboratory parameters during the course of patient's illness

	Day 1	*Day 5*	*Day 10*	*Day 14*
Haemoglobin (g/dl)	3·0	9·5	9·2	6·8
Platelets (× 10⁹/l)	200	61	37	18
MCH (pg)	21·6	27·3	27	28
Reticulocyte count (× 10⁹/l)	26	157	—	81
ESR (mm per hour)	140	—	125	95
Potassium (mmol/l)	5·9	4·0	5·6	4·9
Urea (mmol/l)	30·9	36·1	23·6	33
Creatinine (μmol/l)	249	170	154	306
Bilirubin (μmol/l)	16	48	81	186
Alkaline phosphatase (μ/l)	221	381	352	—
Aspartate aminotransferase (μ/l)	52	63	25	60
Gamma GT (u/L)	40	124	—	—

The patient's haematological findings on admission and during the course of his illness are shown in the table. The direct Coomb's test was strongly positive and urinalysis was normal. The blood film showed polychromasia and spherocytosis but no red cell fragmentation. A few atypical lymphocytes were seen. No malarial parasites were found on multiple smears. The white cell count was 11·3 × 10⁹/l. The reticulocyte response was delayed but later picked up (157 × 10⁹/l). He had hypoalbuminaemia and the lactate dehydrogenase (LDH) level was 213 U/l. A chest radiograph did not reveal any abnormality. An initial diagnosis of auto-immune haemolytic anaemia with uraemia was made. He was transfused with 5 units of cross-matched blood and started on oral prednisolone (60 mg/d) and calcium resonate (for hyperkalaemia). Empirical antibiotic cover was provided with amoxycillin followed by ceftazidime although blood cultures were consistently negative.

Further investigations showed a raised plasma ferritin (1664 μg/l), low serum iron (4·9 μmol/l) and serum transferrin level (1·82 g/l). Serum haptoglobins were absent. No haemoglobinopathies were detected. The coagulation profile was within normal limits. Tests for urinary haemosiderin and bilirubin were negative. Ultrasound examination and CT of the abdomen revealed an enlarged spleen while liver and kidneys were normal. There was no significant lymphadenopathy.

Bone marrow aspiration findings (which were confirmed by trephine biopsy) showed a hypercellular marrow with erythroid hyperplasia and megaloblastic changes. There was no evidence of infiltrative lymphoproliferative disorder although surface marker analysis of blood showed an abnormal proportion of lambda bearing cells with kappa/lambda ratio of 1:6. These abnormalities were thought to reflect dysregulation rather than lymphoid neoplasia. However, the possibility of neoplasia in both B and T cell systems could not be ruled out with certainty. Further investigations for paraprotein analysis and phenotyping could not be performed.

In view of the bone marrow findings a working diagnosis of anaemia due to a combination of autoimmune haemolysis, ineffective erythropoiesis and chronic renal failure was made.

Day 5 The patient was transferred to the care of the HIV team. His general condition had improved after transfusion but he still complained of hiccups. The haemoglobin had improved to 9·5 g/dl. The reticulocyte count was 157 × 10⁹/l. Skin biopsy specimen from

the indurated retro-auricular lesions showed non-specific inflammation. There was no evidence of lymphoproliferative infiltration and special stains for *Rochalimaea henselae* were negative. Potassium, urea and creatinine levels improved. However, bilirubin increased to 48 μmol/l and the platelet count dropped to 37 × 10⁹/l. The plasma D-dimer level was increased (2500 ng/ml; normal less than 250) and a possibility of mild disseminated intravascular coagulation was raised in addition to thrombocytopenic purpura and haemolytic anaemia, probably immune-mediated. The prothrombin time/international normalised ratio was 1·3. Urine output was maintained but urine dipstick test showed glycosuria and no ketones. The peripheral smear showed spherocytes but no red cell fragments.

Day 10 to day 14 The haemoglobin dropped rapidly to 6·8 g/dl. Potassium, bilirubin, urea and creatinine levels rose again. Hyperkalemia was treated with a dextrose-insulin infusion and oral calcium resonate. He was transfused 3 more units of blood. Over the next two days the patient's condition worsened. He became acidotic and succumbed to acute renal shutdown despite aggressive frusemide and dopamine therapy.

Clinical diagnosis:
1. Auto-immune haemolytic anaemia
2. Uraemia (? cause)
3. Thrombocytopenia (? cause)
4. HIV infection

Discussion *(Dr C A Bowman)*

The patient was a 45 year old African man who was moderately immunocompromised with a CD4 count of 0·184 × 10⁹/l. His HIV infection had been asymptomatic until two weeks before admission. He was, however, known to have hypertension and gout. His antihypertensive medication, α-methyldopa, suggests a longstanding hypertension problem. At the time of presentation we note that he had mild uraemia, raised creatinine, hyperkalaemia and anaemia. These findings could be attributed to chronic renal failure, possibly secondary to hypertension. Adrenal insufficiency should also be considered as he presented with vague gastrointestinal symptoms, nausea, abdominal pain and diarrhoea, in addition to anaemia and uraemia. This possibility will also be discussed later.

Summarising his clinical picture: two weeks before admission, the patient developed symptoms of lethargy, weight loss, fever, diarrhoea and shortness of breath. He was normotensive on admission despite a hypertensive past history and not being on any drugs for four months. So, in fact, his blood pressure may have been lower than normal for him. He had hepatosplenomegaly. He also had an elevated ESR of 140 mm at one hour, a profound anaemia—a drop of 4 g/dl in two weeks. He later developed acute renal failure as well.

Let me concentrate on the positive findings. Firstly the skin lesions. He is said to have Kaposi's sarcoma (KS). In the United Kingdom KS is seen mainly in homosexuals, but in Africans KS is commonly found in heterosexual patients. The pattern of KS disease may be different in African patients with atypical and aggressive forms. Some patients have extensive visceral involvement but minimal skin lesions. KS is common in Malawi where the patient comes from and a study from Malawi indicated that KS in HIV positive patients had a very bad prognosis of around 6 months.[1] Other conditions can also cause skin lesions in HIV patients. One of the important conditions missed clinically in patients having KS-like lesions is bacillary angiomatosis. This can cause a systemic illness and can be fatal if untreated. The causative organism, *Rochalimaea henselae*, was not detected. Other important conditions to be considered are cryptococcosis and histoplasmosis, although the patient was probably not immunocompromised enough to have disseminated fungal infection. He is also not from an area endemic for *Histoplasma capsulatum* although Africans may develop a form of histoplasmosis due to *Histoplasma capsulatum var. duboisii*. He would be at risk of disseminated *Pneumocystis carinii* infection which can give rise to KS-like lesions but again he was probably not immunocompromised enough for this or for disseminated *Mycobacterium avium* infection. Tuberculosis should remain high on the list and this will be discussed later.

The profound rapidly progressive anaemia is attributed to auto-immune haemolysis. However, auto-immune haemolytic anaemia (AIHA) is unusual in HIV infected patients.[2] AIHA may be due to lymphoma in HIV infected patients. AIHA can also be caused by α-methyldopa and a number of infections such as mycoplasma pneumonia, infectious mononucleosis.

The patient had a positive Coomb's test. However 20–43% of patients with HIV have a positive Coomb's test at this stage of the disease.[3] It is a non-specific reaction secondary to hypergammaglobinaemia. About 10 to 20% of patients on prolonged α-methyldopa will develop a positive Coomb's test which may remain positive for a variable length of time after stopping of the drug (from weeks up to 28 months).[4] However, the haemolysis associated with α-methyldopa is usually mild and extravascular and ceases rapidly after discontinuation of the drug. So a profound anaemia cannot be explained on this basis.

G6PD deficiency is common in Africans and can lead to haemolytic anaemia. It may be precipitated by intercurrent infections and antioxidant drugs. The patient was not screened for G6PD deficiency, although other haemoglobinopathies were excluded.

Certain non-immune mediated causes of acquired haemolytic anaemia may be considered. He had not been to Africa recently and malaria was adequately excluded. He was probably not immunocompromised enough to have disseminated toxoplasmosis. Gram-negative infections, *Clostridium welchii* infection and

other infections were ruled out by repeated blood cultures.

On admission the bilirubin level was normal which was not compatible with haemolysis as the sole cause of his anaemia. His reticulocyte response was also delayed which may be explained by a hypofunctional marrow. He also had a normal LDH which rules out haemolytic uraemic syndrome. His urine was negative for urobilinogen and haemosiderin which ruled out chronic haemolytic anaemia. Other factors could have contributed to his anaemia. African patients may have extensive visceral KS which may bleed; however, this patient did not have any clinical evidence of haemorrhage.

Bone marrow (BM) aplasia may be secondary to infection. On admission he had anaemia with a WBC count of $11{\cdot}7 \times 10^9$/l and normal platelet count suggesting a selective effect on RBC production. Parvovirus B19 infection can cause erythroid hypoplasia, however, his BM examination showed erythroid hyperplasia. Cytomegalovirus and atypical mycobacterial infection can involve the marrow; however, the patient was not immunocompromised enough for significant reactivation or dissemination of these infections, which occur most commonly at CD4 counts less than 50×10^9/l. The ineffective erythropoieisis seen on bone marrow aspiration may be attributed to his HIV infection, chronic renal failure or it may be secondary to some other process such as chronic infection. On bone marrow examination there was no evidence of any lymphoproliferative or infiltrative disorders but he had increased percentage of lambda cells which would prompt one to look for B-cell lymphoma. The abnormalities were attributed to HIV related dysregulation. His chest radiograph, CT of abdomen and head were normal and a normal LDH level would be against a diagnosis of a lymphoma (LDH is usually significantly raised in lymphoma).

Many conditions may give rise to deteriorating renal functions in an HIV infected individual. HIV associated nephropathy may give rise to chronic glomerulosclerosis and may have an acute phase but this produces a nephrotic syndrome with massive proteinuria and minimal oedema and renal insufficiency.[5] This patient did not have any proteinuria. Sepsis or other intercurrent infection could have led to renal failure. Renal failure could have been secondary to his profound anaemia.

Later the patient developed hyperbilirubinaemia and his liver function deteriorated. This may be due to a hepatitis or a cholangitis or it may be a part of terminal total body failure. So what took him over the edge? Bacterial sepsis? Cultures were persistently negative. It is important to rule out infection as he was susceptible to various infections such as pneumococcus, salmonella and *Clostridium welchii* infection. Serology for various viruses, mycoplasma and other atypical pneumonias was negative. Disseminated *Pneumocystis carinii* infection is unlikely in view of the normal chest radiograph. The patient was not immunocompromised enough for disseminated cryptococcal infection although this possibility should be kept in mind.

This brings us to consider the possibility of miliary tuberculosis (TB). He comes from an endemic area in Africa. Miliary TB can be a very difficult diagnosis to make and often it is made only at necropsy.[6] The symptoms can be vague and the onset insidious. It may cause symptoms of fever, weight loss and malaise. The chest radiograph may be normal in many instances. It is often associated with hepatosplenomegaly. Choroidal tubercles may or may not be present. Skin lesions may be very nonspecific in a nonreactive form of TB. A wide variety of blood dyscrasias may be seen with TB including anaemia, thrombocytopenia and disseminated intravascular coagulation. The white cell count may be normal or decreased. These blood abnormalities may be due to a combination of bone marrow involvement, hypersplenism and sometimes a hypersensitivity effect on the bone marrow. Histopathological examination of skin lesions may be nonspecific because of the non-reactive nature of miliary TB. Results from smears and cultures for acid-fast bacilli were not available. Miliary TB may cause adrenal failure. With chronic adrenal insufficiency one can get symptoms of lethargy, malaise, abdominal symptoms, unexplained fever, a high ESR and uraemia etc. Hyperkalaemia on admission may occur as part of an adrenal crisis. The patient responded to steroids initially and this would fit in with adrenal involvement.

In conclusion my clinical diagnosis would be:

1. Disseminated tuberculosis
2. Secondary adrenal failure
3. HIV infection

Post-mortem examination *(Dr M Carey)*

Post mortem examination showed icterus of both conjuntivae, evidence of a retroauricular skin biopsy and a few small plaques over the upper arms and left thigh. The abnormalities found on internal examination were of old pleural adhesions over the upper lobe of the left lung, tracheobronchitis, pulmonary oedema with patchy consolidation in both lower lobes, marked hepatosplenomegaly (the spleen weighing 800 g) and pale, swollen kidneys. The cardiovascular system, endocrine system and central nervous system were unremarkable and no significant lymphadenopathy was found.

Histology of skin lesions was consistent with Kaposi's sarcoma. In some organs there was an infiltrate of atypical cells mainly present within small blood vessels. These cells were positive for leucocyte common antigen. B and T cell markers were negative, probably because of post mortem autolysis. These findings were those of angiotropic large cell lymphoma. In the lungs there was oedema, but no evidence of infection was found. In places alveolar septae were expanded by aggregates of lymphoma cells within capillaries. In the kid-

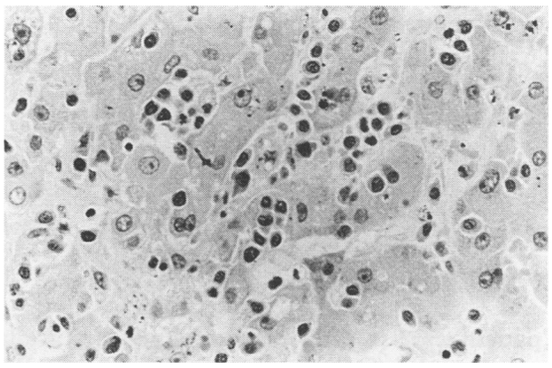

Figure 1 Atypical cells within the hepatic sinusoids.

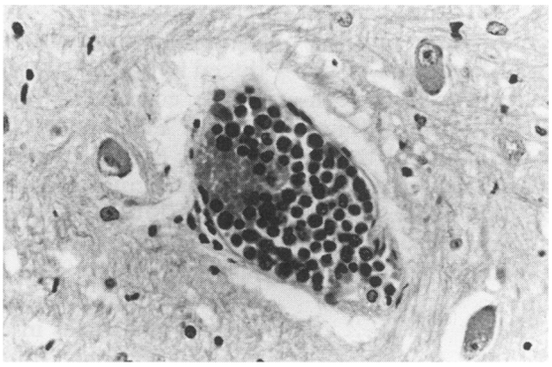

Figure 2 A vessel in the brain stem containing similar atypical cells.

neys, some lymphoma cells were seen within glomeruli and within small vessels of the cortex and medulla. There were numerous lymphoma cells in the sinusoids of the liver and in a few branches of the portal vein (fig 1). A few small vessels in the adrenal glands and brain contained lymphoma cells also (fig 2).

Anatomical diagnosis:
1. Angiotropic large cell lymphoma
2. Kaposi's sarcoma

Conclusion

Angiotropic large cell lymphoma is a rare malignancy that is characterised by a neoplastic proliferation of lymphoid cells within vascular lumina, with little or no adjacent parenchymal involvement. It was originally described in 1959 by Pfleger and Tappeiner[7] who interpreted it as a malignant proliferation of endothelial cells (malignant angioendotheliomatosis). The cells were later found to be lymphoid[8] and it is now known to be a high grade lymphoma of usually B cell lineage.

It commonly affects the central nervous system (progressive dementia, multiple neurological deficits) and the skin (purpura, plaques and nodules) where it was first described, but can affect almost any organ including the lungs, kidneys, liver, adrenal glands, heart and spleen.[9]

The bone marrow is often not involved and tumour cells are rarely found in peripheral blood films, but autoimmune haemolytic anaemia has been described.[9] Cases are often first diagnosed at necropsy. Diagnosis is made by biopsy. The prognosis is poor, but remission has been achieved with combination chemotherapy.

The mechanism causing trapping of the neoplastic cells within blood vessels is not understood, but an abnormality of a surface adhesion molecule on the neoplastic cells or the endothelial cells of certain organs seems likely.

Only one previous case of angiotropic large cell lymphoma in an HIV-infected patient has been reported in the literature. This case also demonstrated cutaneous involvement.[10]

This rare condition can present in a multitude of ways. As well as those mentioned above, it can mimic Kaposi's sarcoma and can produce progressive respiratory or hepatic failure, nephrotic syndrome, Addison's disease, lytic bone lesions, and still birth.

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